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SERUM URIC ACID - A SIGNIFICANT BIOMARKER IN PREECLAMPSIA.

Obstetrics & Gynaecology

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ABSTRACT

The aim of the present study was to determine the relationship between maternal serum uric acid levels and feto-maternal complications in patients with preeclampsia/eclampsia, and to obtain a predictive value of serum uric acid for these complications.

Methods: The present prospective study was conducted over a period of seven months from December 2019 to June 2020. As per the ACOG criteria, 98 patients with preeclampsia/eclampsia were recruited into the study group and divided into two groups- preeclampsia and severe preeclampsia/eclampsia. Serum uric acid levels were determined for all. The outcomes studied were in the form of preterm births, foetal growth restriction (FGR), Apgar score, and foetal deaths.

Results: 98 patients with preeclampsia were included in the study. Uric acid concentration was significantly higher in severe preeclampsia group (5.0125± 1.77 vs 7.352± 1.23; *P*<0.001). Preterm birth was the most common complication, accounting for 57.14% (n=56), followed by FGR at 18.36%. Apgar score of less than 7 was established for 21 live neonates. There were 4 foetal deaths. For individual foetal/neonatal complications, the AUC of uric acid was highest for prognosis of APGAR <7 (AUC 0.767, *P*<0.001), followed by FGR (AUC 0.758, *P*<0.001) and preterm births (AUC 0.753, *P*<0.001). High uric acid level (≥5.6mg/dl) resulted in increased risk of preterm birth (*P*<0.001), low Apgar score (*P*=0.002), FGR (*P*<0.001), and foetal deaths (*P*=0.003).

Conclusion: Maternal serum uric acid concentration is a good predictor of foetal/neonatal outcomes in women with preeclampsia/eclampsia.

KEYWORDS

uric acid, preeclampsia, eclampsia, preterm birth, foetal growth restriction, APGAR.

INTRODUCTION

Preeclampsia is a pregnancy-induced syndrome defined by sudden onset hypertension (≥140 systolic/90 diastolic mm Hg) and proteinuria (>300 mg/24 h) after 20 weeks of gestation. Preeclampsia is estimated to have an incidence of around 2% to 8% of all pregnancies.[1] It continues to be one of the most severe causes of maternal and perinatal morbidity and mortality. There are adverse perinatal outcomes as well, like foetal growth restriction, preterm birth, and intrauterine death. Although the definitive treatment for preeclampsia is to terminate the pregnancy, many pregnant women can be expectantly managed with maternal blood pressure monitoring, foetal monitoring, and seizure prophylaxis. Hence, it is essential to predict preeclampsia and its complications to avoid mortality and morbidity of both the mother and the foetus.

A raised uric acid level is one of the significant findings in preeclampsia. Uric acid is produced as a result of purine degradation, catalysed by the enzyme xanthine oxidase. In normal pregnant women serum uric acid concentration initially falls by 25-30% due to elevation in renal clearance secondary to increased GFR or reduced proximal tubular reabsorption due to changes in its production rate. Later in pregnancy, the serum uric acid levels increase due to foetal production, decreased uric acid clearance and decreased binding to albumin.[2] Hyperuricemia in preeclamptic women is primarily caused by reduced glomerular filtration rate due to endothelial dysfunction.[3,4] Uric acid is a potent inflammatory mediator and it stimulates monocytes to produce pro-inflammatory cytokines. Uric acid promotes endothelial dysfunction which can promote hypertension, renal disease and vascular disorders.[5] Many studies have reported elevated uric acid levels to be correlated positively with adverse maternal and foetal outcomes.[6,7] However, others state that raised uric acid level is a poor predictor of maternal and foetal outcomes.[8,9] Therefore, the present study was designed to assess the association of uric acid levels with severity of preeclampsia and its relation to fetomaternal outcomes.

AIM:

The aim of the present study was to determine the relationship between maternal serum uric acid levels and fetomaternal complications in patients with preeclampsia/eclampsia, and to obtain a predictive value of serum uric acid for these complications.

MATERIALS AND METHODS:

The present prospective study was conducted over a period of seven months from December 2019 to June 2020 and included all pregnant women ≥28 weeks of gestation with the diagnosis of preeclampsia, severe preeclampsia or eclampsia admitted in the Obstetrics and Gynaecology department of Kempegowda Institute of Medical Sciences Hospital, Bangalore.

Patients with a history of pre-existing medical disorders such as type II diabetes mellitus, chronic hypertension, renal disease, liver disease, as well as any cardiovascular, thyroid, or other endocrinologic disorders were excluded from the study.

Preeclampsia was diagnosed based on the "ACOG Task Force on Hypertension in Pregnancy 2013"[10] as follows: women known to be normotensive who developed a systolic BP≥140mm Hg or diastolic BP≥90mm Hg on two occasions at least 4hours apart after the 20th week of gestation and proteinuria ≥300mg/24 h urine collection or a protein/creatinine ratio ≥0.3. In the absence of proteinuria, preeclampsia was diagnosed as hypertension with new-onset thrombocytopenia, elevated liver transaminase levels, renal insufficiency, pulmonary edema, and/or now-onset cerebral or visual disturbances. For severe preeclampsia, the features were any of the following- systolic blood pressure of 160 mm Hg or more, or diastolic blood pressure of 110 mm Hg or more on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time), thrombocytopenia (platelet count less than 100,000/mm^3 , impaired liver function that is not accounted for by alternative diagnoses and as indicated by abnormally elevated blood concentrations of liver enzymes (to more than twice the upper limit normal concentrations), or by severe persistent right upper quadrant or epigastric pain unresponsive to medications, renal insufficiency (serum creatinine concentration more than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease), pulmonary oedema, new-onset headache unresponsive to medication and not accounted for by alternative diagnoses, visual disturbances.[11] Preeclampsia with occurrence of convulsions constitutes eclampsia.

Recruited subjects were divided into two groups, that is, preeclampsia as group 1 and severe preeclampsia/ eclampsia as group 2. The serum uric acid levels were estimated along with other relevant investigations for all patients and were recorded. The general characteristics such as age, parity and BMI were recorded. The maternofoetal outcomes in terms of preterm birth, presence of foetal growth restriction (FGR), APGAR score and foetal deaths (which included intrauterine demise and still births) were noted.

All analyses were performed using MedCalc version 19.4 (MedCalc Inc., Ostden, Belgium). Receiver operating characteristic (ROC) curves were constructed to determine the diagnostic test performance

of uric acid for the prognosis of each outcome. General complications constituted the occurrence of at least one of the four events, that is, preterm birth, APGAR score less than 7 in the first minute, foetal death and FGR.

RESULTS:

During the study period, 98 pregnant women with pre-eclampsia/ eclampsia, who met the eligibility criteria, were recruited consecutively.

The general characteristics of the study group and the foetal complications are shown in Table 1. The mean age of the study participants was 26.69±4.67 years, and there was no significant difference in age between group 1 (preeclampsia) and group 2 (severe preeclampsia/eclampsia). Differences in parity and BMI were also insignificant between the two groups. Uric acid concentration was significantly higher in group 2 compared with group 1 (5.0125± 1.77 vs 7.352± 1.23; *P*<0.001).

Table 1 - General characteristics of the study population and foetal/neonatal outcomes

Characteristics	Group 1: preeclampsia (n =48)	Group 2: severe preeclampsia/eclampsia (n =50)	Total N=98	P value
Maternal age(years)	29.96 ± 4.34	30.12 ± 5.34	26.69±4.67	0.72
Parity				0.78
Nulliparous	26 (54.16%)	23 (46%)	49(50%)	
Multiparous	22 (45.83%)	27 (54%)	49(50%)	
BMI(kg/m^2)	26.34 ± 2.95	26.32 ± 3.12	26.3± 3.12	0.62
Uric acid (mg/dl)	5.0125±1.77	7.352± 1.23		<0.001
Preterm birth	14 (29.16%)	42 (84%)	56(57.14%)	<0.001
Apgar score <7	2(4.16%)	19 (41.3%) (among n=46 live births)	21(22.34%)	<0.001
Foetal death	0	4 (8%)	4(0.04%)	0.004
FGR	0	18 (36%)	18(18.36%)	<0.001

Preterm birth was the most common complication, accounting for 57.14% (n=56), followed by FGR at 18.36%. Apgar score of less than 7 was established for 21 live neonates. There were 4 foetal deaths.

For individual foetal/neonatal complications, the area under the curve (AUC) of uric acid was highest for prognosis of APGAR <7 (AUC 0.767, *P*<0.001), followed by FGR (AUC 0.758, *P*<0.001) and preterm births (AUC 0.753, *P*<0.001) (Table 2).

Table 2 - Criterion values, sensitivity, and specificity of serum uric acid concentration as markers for prognosis of foetal/neonatal complication

Complications	Criterion of uric acid(mg/dL)	Sensitivity	Specificity	AUC	*P* value
Preterm birth	>5.8	65.2	78.6	0.753	<0.001
APGAR <7	>5.6	65.2	74.2	0.767	<0.001
Foetal death	>5.6	87.6	69.2	0.723	0.169
FGR	>5.6	71.9	69.8	0.758	<0.001

Table 2 - Criterion values, sensitivity, and specificity of serum uric acid concentration as markers for prognosis of foetal/neonatal complication

In general, the AUC was 0.846 and the threshold uric acid level was 5.6mg/dl, with 94% sensitivity and 70.8% specificity (Fig. 1).

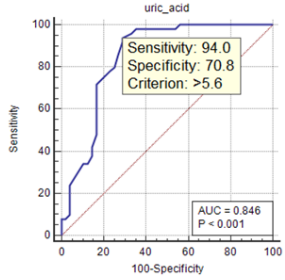

Figure1.

The relationship between foetal outcomes and uric acid threshold of 5.6mg/dl is shown in Table 3. High uric acid level (≥5.6mg/dl) resulted in increased risk of preterm birth (*P*<0.001), low Apgar score (*P*=0.002), FGR (*P*<0.001), and foetal deaths (*P*=0.003). There was no association between uric acid level and maternal factors such as age and parity (Table 4). The only associated factor was severe preeclampsia/eclampsia (*P*<0.001).

Table 3 - Relationship between foetal outcomes and uric acid threshold of 5.6 mg/dL

Outcomes	Uric acid ≥5.6 mg/L (n=63)	Uric acid <5.6 (n=35)	*P* value
Preterm birth	48 (76.19%)	8 (22.85%)	<0.001
Apgar <7	18 (28.57%)	1 (2.85%)	0.002
Foetal death	4 (63.49%)	0	0.003
IUGR	17 (26.98%)	1 (2.85%)	<0.001

Table 4 - Relationship between uric acid levels and maternal factors

Maternal factors	Uric acid ≥5.6mg /dL(n=63)	Uric Acid <5.6 mg/dL(n=35)	*P* value
Maternal age, y			0.725
≥35 (n=10)	3 (30%)	7 (70%)	
<35 (n=88)	60 (68.18%)	28 (31.82)	
Parity			0.642
Multiparous (n=49)	31 (63.26%)	18(36.73%)	
Nulliparous (n=49)	32 (65.30%)	17 (34.69%)	
Pre– eclampsia/ eclampsia grade			<0.001
Severe pre– eclampsia/eclampsia (n=50)	48 (96%)	2(4%)	
Preeclampsia (n=48)	15 (31.25%)	33(68.75%)	
Total (n=98)	63 (64.28%)	35 (35.71%)	

DISCUSSION

The association of biomarkers, including uric acid, with adverse outcomes in pre-eclamptic pregnant women is discussed in ACOG guidelines[10]; however, its utility as a diagnostic marker is still debated. Many studies suggest that raised serum uric acid in pregnancy may not only be a valuable biomarker for preeclampsia but may also have a role in the pathogenesis of the maternal and foetal manifestations. Uric acid is found to be a potent inhibitor of endothelial function. It induces systemic and glomerular hypertension in animals, and freely passes into the foetal circulation.[12] It plays a direct role in blocking foetal angiogenesis, leading to small-for-gestational-age infants.[13] Uric acid is noted to block trophoblast invasion in vitro.[14,15] Thus, it is time to carefully revisit the role of uric acid as a possibly modifying factor in the pathogenesis of this important disease.

During early pregnancy, uric acid levels reduce, often to ≤3 mg/dL, due to the uricosuric effects of oestrogen and the increase in renal blood flow. Uric acid levels rise thereafter during the third trimester, reaching levels of 4 to 5 mg/dL by term.[12]

Patients with preeclampsia frequently have significantly raised serum uric acid levels, and as per some studies, the degree of elevation correlates with the severity of the maternal syndrome and foetal morbidity, including FGR and foetal death.[16]

In our study, 98 pregnant women diagnosed to have preeclampsia, who satisfied the inclusion criteria, were divided into two groups, that is, preeclampsia and severe preeclampsia/eclampsia . The average age was 26.69±4.67 like other similar studies by Tam Le et al[17] and Reddy et al.[18] Uric acid concentration was significantly higher in those with severe preeclampsia/eclampsia compared with mild preeclampsia group (5.0125± 1.77 vs 7.352± 1.23; *P*<0.001). This is similar to the study done by Mustaphi et al, which states that the mean uric acid level in normotensive pregnant women was 4.65mg/dl±0.33, while it was 5.42mg/dl±0.55 in those with mild preeclampsia and 6.65mg/dl±0.60 in those with severe preeclampsia.[19]

In our study, for general foetal/neonatal complications, the AUC was 0.846 , with the threshold uric acid value being 5.6mg/dL, with 94% sensitivity and 70.8% specificity. As per the study by Johnson et al,[19] uric acid levels conferred an 8- to 9-fold risk for preeclampsia and a 1.6- to 1.7-fold risk for foetal growth restriction. A receiver operating

characteristic analysis stated that uric acid level of 5.2 mg/dL conferred excellent sensitivity, specificity, and likelihood ratios for diagnosis and prognosis, the uric acid level being slightly less than that of our study. In a study done by Ryu et al,[20] best threshold level of maternal uric acid for predicting adverse foetal outcome like low birth weight was found to be 6.35mg/dL (sensitivity, 0.58; specificity, 0.95). Similarly, Hawkins et al reported that maternal hyperuricemia was associated with low birth weight and uric acid value >5.9mg/dL was associated with adverse perinatal outcomes, the value being similar to that obtained in our study.[21] As per the study of Tam Le et al[17] , receiver operating characteristic curve showed that a serum uric acid threshold of 393 µmol/L was a good predictor of general foetal/neonatal complications (AUC 0.752), with 64.4% sensitivity and 79.5% specificity, in women with pre-eclampsia/eclampsia.

In our study, preterm birth was the most common complication, accounting for 57.14% (n=56), followed by IUGR at 18.36% . Apgar score of less than 7 was established for 21 live neonates. There were 4 perinatal deaths. The occurrence of pregnancy outcomes in the present study tam le were: preterm birth rate (22.4%), IUGR (25.9%), Apgar score less than 7 (9.0%), foetal death (2.9%), and neonatal death (4.9%).[17]

Other studies have reported similarly, with preterm birth ranging from 15% to 67%, IUGR ranging from 10% to 25%, and foetal mortality ranging from 1% to 2%.[4]

In our study, for individual foetal/neonatal complications, the AUC of uric acid was highest for prognosis of APGAR <7 (AUC 0.767, *P*<0.001), followed by IUGR (AUC 0.758, *P*<0.001) and preterm births(AUC 0.753, *P*<0.001) .Tam le et al study stated that the AUC of uric acid was highest for the prognosis of neonatal death, followed by preterm birth, Apgar score less than 7, and IUGR.[17]

As reported by Kondareddy T et al,[18] pre-eclamptic women with high uric acid levels had increased risk of adverse outcomes like preterm birth than pre-eclamptic women whose uric acid levels were normal, the reference value being >6.0mg/dl. This is on similar lines with our study, where preeclamptic women with uric acid levels higher than 5.6mg/dl have significantly higher risks of having adverse outcomes such as preterm births, babies with Apgar<7, foetal demise and FGR.

CONCLUSION

To conclude, maternal serum uric acid level was a good prognostic factor for monitoring and prognosis of foetal/neonatal outcomes in women with pre-eclampsia/eclampsia. There was a relationship between high uric acid level and the risk of preterm birth, low Apgar index, FGR, and neonatal death, but not foetal death.

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